

**REMARKS****Rejection of Claims 1-18 and 62 Under 35 U.S.C. § 103 (a)****1. Summary of the Examiner's Rejection**

The Office Action rejects Claims 1-18 and 62 as being unpatentable under 35 U.S.C. § 103 (a) over U.S. Patent No. 6,303,301 to Mack in view of Mangiameli *et al.* (European J. Operational Research, Sept. 1996, Vol. 93, pgs 402-417). The Office Action "is reiterated from the previous Office Action" mailed on December 5, 2003 and states that Mack's method "comprises receiving gene expression values of datapoints, clustering the datapoints, and providing output display indicating the cluster of the datapoints." The Office Action states that Mack does not explicitly disclose clustering using SOMs.

The Office Action states that Mangiameli *et al.* applied the SOM method as well as seven other hierarchical methods of clustering to multiple data sets with real-world data imperfections and concluded that SOM is superior to the other clustering methods.

The Office Action further states that the fact that Mangiameli *et al.* compared SOM to other clustering methods indicates that SOM is an art recognized equivalent of other clustering methods. The Office Action concludes that since Mangiameli *et al.* demonstrated superiority of SOM for data analysis, one of ordinary skill in the art would have been motivated to modify Mack to use SOM for gene expression data. The Office Action also states that there would have been a reasonable expectation of success of modifying Mack with the teaching of Mangiameli *et al.* because Mangiameli *et al.* used data derived from various sources.

**2. Examiner Failed to Give Sufficient Weight to the Declaration of Dr. Kreiman**

As noted in the Reply to the Office Communication mailed from the U.S. Patent and Trademark Office on March 3, 2004 and the Reply to the Office Action mailed on February 11, 2003, the Declaration under 37 C.F.R. 1.132 by Dr. Kreiman reveals that there was no motivation for a person of ordinary skill in the art to combine the Mack and Mangiameli *et al.* references. Dr. Kreiman, an expert in the field, stated in paragraph 8 of the Declaration that he would not have combined the Mack reference with the Mangiameli reference. The Examiner failed to give this Declaration adequate weight and erred by not properly considering the implications presented within the Declaration.

“Firsthand practical knowledge of unsolved needs in the art, by an expert, is evidence of the state of the art.” *In re Piasecki*, 745 F.2d 1468, 1473 (Fed. Cir. 1984). Dr. Kreiman is an expert with such firsthand practical knowledge; however, the Examiner simply dismissed his Declaration as “not persuasive”. The Examiner failed to acknowledge that this Declaration provided evidence that there was no actual motivation to combine. Instead, the Examiner impermissibly rejected the conclusions made by Dr. Kreiman.

Assuming, *arguendo* that the examiner has established a *prima facie* case of obviousness, once the Applicant proffers some evidence rebutting the *prima facie* case, the “decision-maker must start over” and the rejected claims “must be reconsidered in the light of all the evidence.” *In re Rinehart*, 531 F.2d 1048, 1052 (CCPA 1976). The Examiner did not do that in this case. Instead, the Examiner erroneously considered whether the Declaration was strong enough to “knock down” his conclusion of obviousness. “[T]he *prima facie* case is not a stone wall against which rebuttal evidence is tested; patentability is determined by a preponderance of all the evidence.” *In re Glaug*, 283 F.3d 1335, 1338 (Fed. Cir. 2002).

Furthermore, the Examiner has failed to establish that there is an actual motivation to combine within either reference. The Examiner states that the motivation to combine comes mainly from Mangiameli *et al.* because the reference “demonstrates the superiority of SOM ... in data analysis [and] one of ordinary skill in the art would have been motivated to modify Mack to use SOM”. “The question under § 103 ... is not whether one skilled in the art doing what appellant did would have discovered what appellants discovered, but whether it would have been obvious to one of ordinary skill in the art to do what appellants did.” *In re Oelrich*, 579 F.2d 86, 92 (CCPA 1978). Mangiameli *et al.* is a highly technical text on Mathematical Statistics, while Mack discloses methods of “decipher[ing] the complex regulatory relationship among genes” (column 1, line 67 to column 2, line 1). Neither of these references provide any actual motivation for one of ordinary skill in the art to combine the above teachings for use in gene expression analysis as contemplated by the claimed invention.

To summarize, the Examiner did not give sufficient weight or analysis to the Declaration of Dr. Kreiman. Furthermore, neither Mangiameli *et al.* nor Mack nor any other art of record teach or suggest that the SOM method can be successfully applied to gene expression analysis as opposed to Mack’s gene regulatory relationship determination as in the claimed invention.

### 3. Secondary Considerations Refute Obviousness

The Federal Circuit has found that “evidence rising out of the so-called “secondary considerations” must always when present be considered en route to a determination of obviousness.” *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983). Evidence of copying by others and of a long-felt need for an invention are indicative of nonobviousness. See *Graham v. John Deere Co.*, 383 U.S. 1 (1966). Additionally, the Federal Circuit has treated enthusiastic reactions to an invention and peer recognition as secondary considerations that must be considered when determining obviousness. *In re Frank*, 745 F.2d 1468, 1471 (Fed. Cir. 1984).

In this case, the Declaration of Dr. Kreiman and a number of scientific publications demonstrate that there was copying of the claimed method by other scientists, that there was a long-felt need solved by this invention, that there was an enthusiastic reaction to the invention, and that the inventors have been recognized by their peers.

In Paragraph 11 of his Declaration, Dr. Kreiman notes that the claimed invention solves a number of long-felt needs in the field and that the invention has been “a very valuable and novel tool” in the field of bioinformatics.

At least 3 scientific publications credit the inventors for introducing SOMs to the analysis of microarray data. (See Kaminski *et al.*, American J. of Respiratory Cell and Molecular Biology, 2002, Vol. 27, pp. 125-132; Caetano *et al.*, Proceedings of the 7<sup>th</sup> World Congress on Genetics Applied to Livestock Production, Montpellier, France; and The American Thoracic Society available at <http://www.thoracic.org/geneexpress/gene0602.asp>.) Additionally, at least 4 scientific publications reveal that other scientists are copying the claimed method. (See Kaminski *et al.*; Caetano *et al.*; Quakenbush, June 2001, Vol. 2, pp. 418-427 available at [www.nature.com/reviews/genetics](http://www.nature.com/reviews/genetics); and Gibbons *et al.*, Genome Research, 2002, Vol. 12, pp. 1574-1581.)

“[E]vidence of secondary considerations may often be the most probative and cogent evidence in the record”. *Stratoflex*, 713 F.2d at 1538. Accordingly, Applicant believes that once the Examiner reviews the above publications and considers all the evidence presented, the Examiner will find that the invention is not obvious over Mack and Mangiameli *et al.*

**CONCLUSION**

In view of the above remarks, it is believed that all claims (1-18 and 62) are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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